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Progress Toward a Novel Synthesis of the C5 Methylated Cyclopenta[C]pyridine Substructure

Nat Fox

Progress Toward a Novel Synthesis of the C5 Methylated Cyclopenta[C]pyridine Substructure

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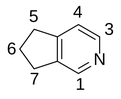
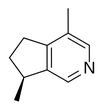
Abstract

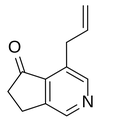
Members of a small family of monoterpene alkaloids containing the cyclopenta[C]pyridine substructure have been identified as natural products from a variety of plant, animal and bacterial sources. Actinidine, the first representative natural product of this family to be described, is produced by several plant species and is present in the semiochemical repertoire of several insects including stick insects, ants, and beetles.[1] As many of the natural products in this family display interesting biological activities, we were motivated to develop a general synthesis for molecules containing the cyclopenta[C]pyridine substructure. Our method employs easily-prepared linear 1,8-enedial precursors that undergo a tandem enamine-enal cycloaddition / pyridine reaction to produce the target molecules.[2] Described here is the current progress in examining the performance of the carbon-5 methylated linear precursor as part of defining the scope and limitations of this general methodology.



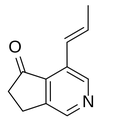
cyclopenta[C]pyridine substructure



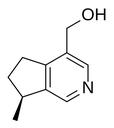
Actinidine



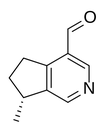
Louisianin C[3]



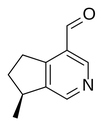
Louisianin D[3]



(-)-Tecostidine[4]



(+)-Boschniakine[5]



(-)-Indicaine[4]

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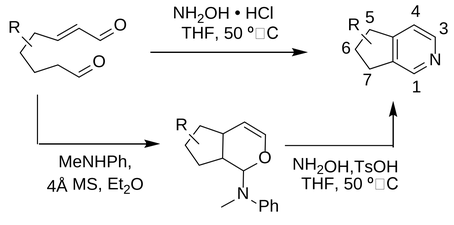
Background and Preliminary Work

Tandem Method



Sequential Method

Isolated Yields Of Substituted Cyclopenta[C]Pyridine[6]

Substrate Me Position	Tandem Method	Sequential Method
Unadorned	20%	33%
C1	NR	NR
C3	31%	26%
C4	56%	40%
C5	??%	??%
C6	35%	12%
C7	43%	??%
C7+C4	70%	49%

Background and Preliminary Work

-Established methods to form the cyclopenta[c]pyridine moiety involve either formation of a substituted cyclopentane followed by cyclization of the pyridine,[6] or creation of a decorated pyridine followed by a closure of the cyclopentane ring.[7]

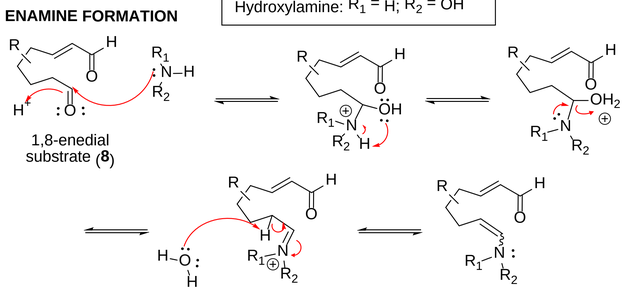
-The method we are exploring utilizes both a tandem and a sequential synthesis of both rings in the desired substructure.

-Others in the Hofferberth group have measured yields for several methyl substituted targets, but the performance of the C5 methyl substituted substrate in generating the corresponding cyclopenta[C]pyridine has yet to be examined. The operation of unexpected side reactions have hindered the synthesis of the requisite C5-methylated substrate.

Proposed Mechanism of Key Step

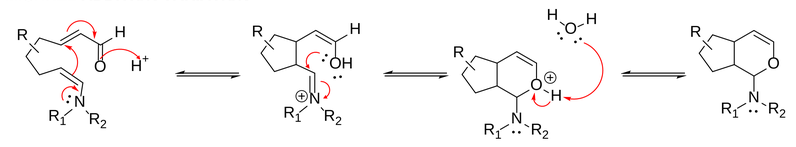
N-methylaniline: R_1 = CH_3; R_2 = Ph
Hydroxylamine: R_1 = H; R_2 = OH

ENAMINE FORMATION

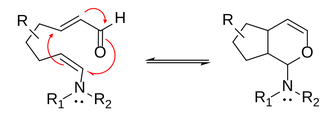


1,8-enedial substrate (**8**)

MICHAEL ADDITION VARIATION

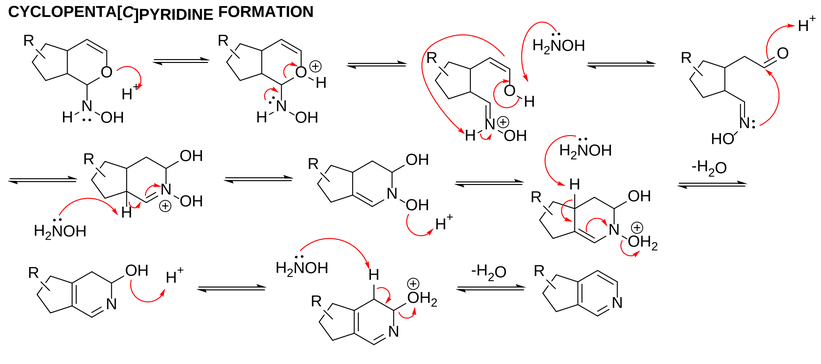


CYCLOADDITION VARIATION[6]

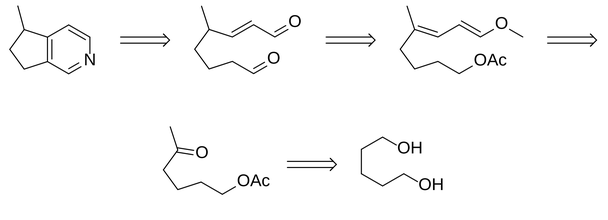


13: R_1 = CH_3; R_2 = Ph
13a: R_1 = H; R_2 = OH

CYCLOPENTA[C]PYRIDINE FORMATION

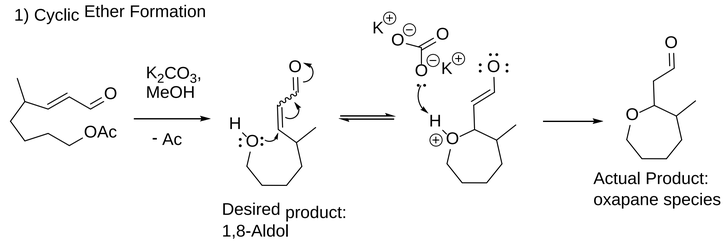


Retrosynthetic Analysis

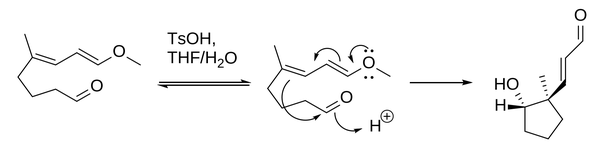


Unexpected Challenges

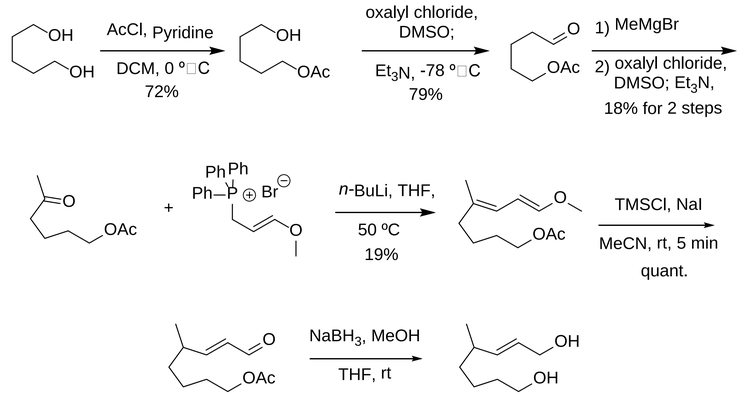
1) Cyclic Ether Formation



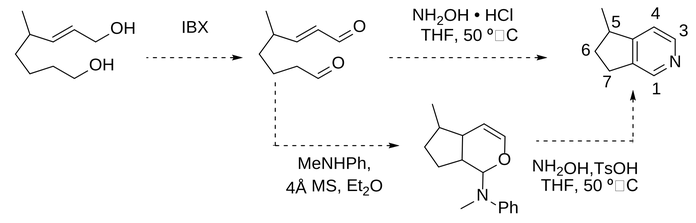
2) Vinylogous Aldol Reaction



Current Progress



Future Work



Acknowledgements

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